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Low Cholesterol, Mortality, and Quality of Life in Old Age During a 39-Year Follow-Up

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OBJECTIVES We assessed the impact of serum cholesterol level in early midlife on total mortality during up to 39 years of follow-up and on the quality of life (QoL) in old age.

BACKGROUND Total effects of low serum cholesterol on health have been in dispute, especially in elderly persons, and there are few data on the long-term effects of low cholesterol on QoL.

METHODS The cohort consisted of 3,277 healthy businessmen age 30 to 45 years at baseline (1960s). In addition to baseline, serum cholesterol values were available for part of the cohort in 1974, 1986, and 2000. The QoL was assessed in 80.9% of survivors (n = 1,820, mean age 73 years) with a RAND-36 (SF-36) QoL questionnaire in 2000. Mortality up to 2002 (n = 1,173) was retrieved from national registers.

RESULTS Cholesterol was clearly reduced in survivors during follow-up, except in the lowest baseline serum cholesterol group. Baseline cholesterol predicted 39-year total mortality in a graded manner ($p < 0.0001$), and a value ≤5.0 mmol/l was associated with a 25% reduction in total mortality. In old age, the physical component summary score of RAND-36 was significantly ($p = 0.02$) higher (better) in the lowest baseline cholesterol group; no difference was found in the mental component summary score ($p = 0.51$).

CONCLUSIONS Low serum cholesterol level in midlife predicted not only better survival but also better physical function and QoL in old age, without adversely affecting mental QoL. (J Am Coll Cardiol 2004;44:1002–8) © 2004 by the American College of Cardiology Foundation

The research behind the current goals of hypolipidemic therapy is extensive (1,2), and the cardiovascular benefits of cholesterol lowering for five to seven years have been repeatedly demonstrated (2). Still, there have been controversies regarding the truly long-term prognostic value of low cholesterol on total mortality, especially in older individuals

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(3–5). Also the long-term effects of low (or lowered) cholesterol on mental functioning and quality of life (QoL) have been in dispute (6,7). Because there are now efficient drugs to bring cholesterol to low levels, we still need long-term data to show that low cholesterol is not harmful. We present the results on a large group of men who were initially healthy, age 30 to 45 years, and whose baseline cholesterol was related not only to total mortality during up to 39 years of follow-up but also to health-related QoL in old age. It should be noted that our study essentially reflects the association of naturally (or lowered by secular changes) low cholesterol levels with mortality because the effects of cholesterol-lowering drugs are largely restricted to the last years of follow-up.

METHODS

Baseline examinations in 1968 to 1973 and follow-up examinations in 1974 and 1985. The study population and examinations have been described in detail (8–11), and a flow chart of examinations pertaining to cholesterol is shown in Figure 1. The follow-up data are comprehensive at baseline and at the end, whereas the three in-between evaluations include only part of the population.

A total of 3,490 initially healthy men, mostly business executives born in 1919 to 1934, participated in voluntary health check-ups from 1964 to 1973 (median 1968) at the Institution of Occupational Health in Helsinki, Finland. At that time occupational health care was not customary in Finnish companies. The health check-up procedures included clinical examinations and laboratory tests. Ergometry was performed, but data were not entered into the database and are thus not available for analysis. Only one baseline measurement of serum cholesterol is available, and between baseline and the 2000 survey only mortality data were collected systematically from all participants. The first scientific approach (8) was performed in 1974, when the men consented to an evaluation in which electrocardiographic findings were correlated to risk factors (including cholesterol) and coronary heart disease. The men were also evaluated with mailed questionnaires and laboratory exam-

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Abbreviations and Acronyms

MCS = mental component summary
PCS = physical component summary
QoL = quality of life
SF-36 = Short Form-36

inations in order to find healthy participants for a primary prevention study (9). In the questionnaires, 2,696 of the men (77%) rated their current health and physical fitness on a five-step scale ("very good," "good," "fair," "poor," or "very poor"). In 1974, fasting serum cholesterol was measured in healthy candidates for the intervention trial (n = 2,245), and 1,709 of these men were further contacted in 1985 with questionnaires and laboratory examinations (cholesterol measurement in 1,246 men). In contrast to earlier examinations, cholesterol values in 2000 were based on self-report in questionnaires sent to all survivors of the initial cohort.

The present study on mortality and cholesterol includes the 3,277 men (94 %) for whom baseline serum cholesterol measurements were available. Exclusion of the 612 men who participated in the 5-year intervention trial during the 1970s (9) did not alter the conclusions of the present study, and therefore the results of the whole original cohort are presented.

During the 1960s and 1974, serum cholesterol concentration was determined using the method of Huang et al. (12); since then routine laboratory analyses with enzymatic methods have been used. According to our measurements

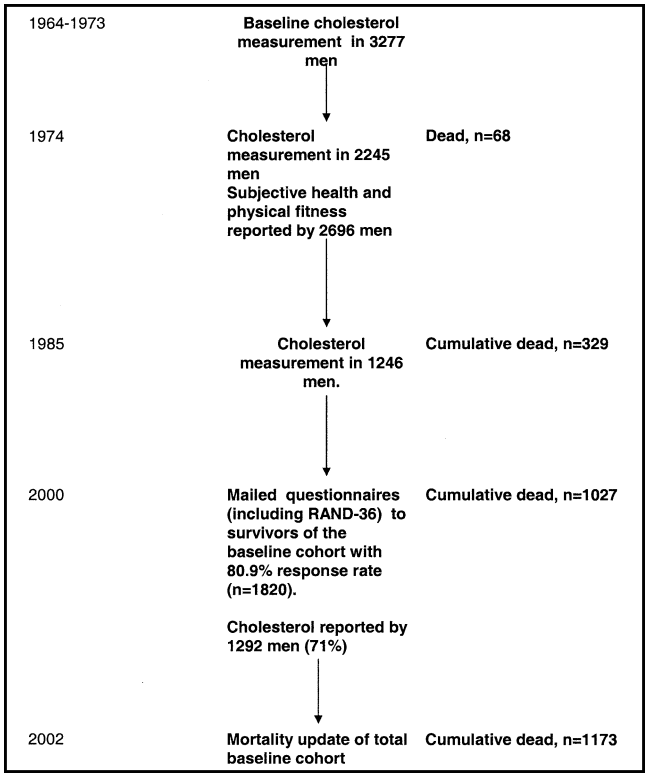

Figure 1. Flow chart of the study.

(10), cholesterol levels measured with older methods gave 8.3% higher values. Accordingly, 5.0 mmol/l in the 1960s would correspond to 4.6 mmol/l measured with an enzymatic method. We used the corrected values in the present analyses; the conclusions nevertheless remained the same when original values were used. In some of the analyses we compared the lowest cholesterol group (≤5.0 mmol/l, n = 224) with other groups combined.

The 2000 survey. In 2000, we sent a mailed questionnaire (re-mailed once for non-respondents) to all survivors of the original cohort, and 1,820 of 2,251 men (80.9%) responded. The questionnaire included items on demographic variables and lifestyle (smoking, alcohol consumption, physical activity), history of diseases, and the latest serum cholesterol level. In addition, the Finnish version of the RAND-36-Item Health Survey 1.0 (practically identical to the SF-36 health survey) (13–15) was embedded in the questionnaire. The RAND-36 questionnaire has been validated in the Finnish population (13).

Mortality follow-up. Total mortality of the study population was regularly recorded until December 31, 2002. The mortality data were retrieved (after approval) from Statistics Finland and the Central Population Register, which keeps a registry of all Finnish citizens. According to the Register, assessment of vital status is very reliable for people having their permanent place of residence in Finland (more than 95% of the present cohort in 2000), regardless of whether they die in Finland or abroad. Moreover, assessment of the vital status is also quite reliable for Finnish citizens living permanently abroad. Because the study population was defined as those who were born in 1919 through 1934 and attended at least one health check-up between the years 1964 and 1973, the total follow-up time of the cohort is up to 39 years (median 35 years, interquartile range 33 to 37 years).

Statistical methods. Number Crunching Statistical System statistical software (Kaysville, Utah) was used for the analyses. In most analyses we compared the lowest baseline serum cholesterol group (≤5.0 mmol/l, n = 224) with other groups combined. However, we also present survival analyses according to the baseline cholesterol values divided into per 1 mmol/l increasing groups (i.e., ≤5.0 mmol/l [n = 224], 5.1 to 6.0 mmol/l [n = 803], 6.1 to 7.0 mmol/l [n = 1,170], 7.1 to 8.0 mmol/l [n = 720], 8.1 to 9.0 mmol/l [n = 255], and >9.0 mmol/l [n = 105]). The *t* tests, nonparametric tests, and analysis of covariance were used where appropriate to compare continuous variables; chi-square tests were used to compare proportions. Differences in survival curves were analyzed with log-rank tests. Relative hazards with their 95% confidence intervals for mortality associated with baseline serum cholesterol were calculated using Cox's proportional hazards regression. Other risk factors were adjusted for in respective models. The eight RAND-36 scales (physical function, role physical, bodily pain, general health, vitality, social function, role emotional, and mental health) were calculated from questionnaires

Table 1. Risk Factors at Baseline in the Study Population

	All (n = 3,277)	Cholesterol ≤ 5.0 mmol/l (n = 224)	Cholesterol ≥ 5.0 mmol/l (n = 3,053)	p Value Between Cholesterol Groups
Age (in 1964), yrs	38 (4)	37 (4)	38 (4)	<0.0001
Body mass index, kg/m^2	26 (3)	26 (3)	26 (3)	0.19
Systolic blood pressure, mm Hg	136 (16)	133 (17)	136 (16)	0.003
Diastolic blood pressure, mm Hg	86 (11)	85 (12)	87 (11)	0.02
Cholesterol, mmol/l	6.6 (1.2)	4.6 (0.4)	6.8 (1.1)	<0.0001
1-h glucose, mmol/l	6.3 (1.9)	6.1 (1.7)	6.4 (1.9)	0.05
Smokers, %	41	38	41	0.45

Data indicate mean (SD) unless otherwise indicated.

(13,14). From these scales, the physical component summary (PCS) and the mental component summary (MCS) scores were calculated of the RAND-36 scales as instructed (15). In statistical analyses two-tailed tests were used, and P values <0.05 were taken as statistically significant.

RESULTS

Baseline characteristics and cholesterol tracking. At baseline, the average age of the cohort (n = 3,277) was 37.3 years, and 44.9% were smokers. All were clinically healthy and without cardiovascular diseases or diabetes. Clinical characteristics at baseline with comparisons between the low-cholesterol group (median serum cholesterol 4.7 mmol/l, interquartile range 4.4 to 4.9 mmol/l) and others are shown in Table 1. In 1974, the distributions of subjective health and physical fitness did not differ between the low-cholesterol group and other groups combined: the p values for the overall differences between the groups were 0.37 (subjective health) and 0.75 (physical fitness). Only 6.3% and 6.6% of the men in the lowest cholesterol group and others, respectively, reported their subjective health as "poor" or "very poor." The respective proportions were 14.9% and 16.2% for physical fitness. Cholesterol values tracked reasonably well during the long follow-up. Analysis of the survivors who reported their cholesterol value in 2000 (n = 1,292) showed that the baseline differences had been sustained over the years, although the values had decreased except in the lowest baseline cholesterol group (Fig. 2).

Mortality during follow-up. During the follow-up there were 1,173 deaths (35.8%), and there was a graded association between mortality risk and baseline serum cholesterol. Survival curves of all baseline cholesterol groups and the lowest baseline cholesterol group (≤5.0 mmol/l) versus other groups combined are shown in Figures 3A and 3B, respectively. Differences were highly statistically significant according to log-rank tests. The curves demonstrate that the survival benefit in the lowest cholesterol group was even accentuated during the last years of the follow-up. Splitting the lowest cholesterol group in half (<4.7 mmol/l, n = 114, and 4.7 to 5.0 mmol/l, n = 110) did not show further reduction of mortality risk (mortality 27.2% vs. 24.5%, respectively; p = 0.76 between the lowest groups), but the numbers were small. In multivariate analyses adjusted for

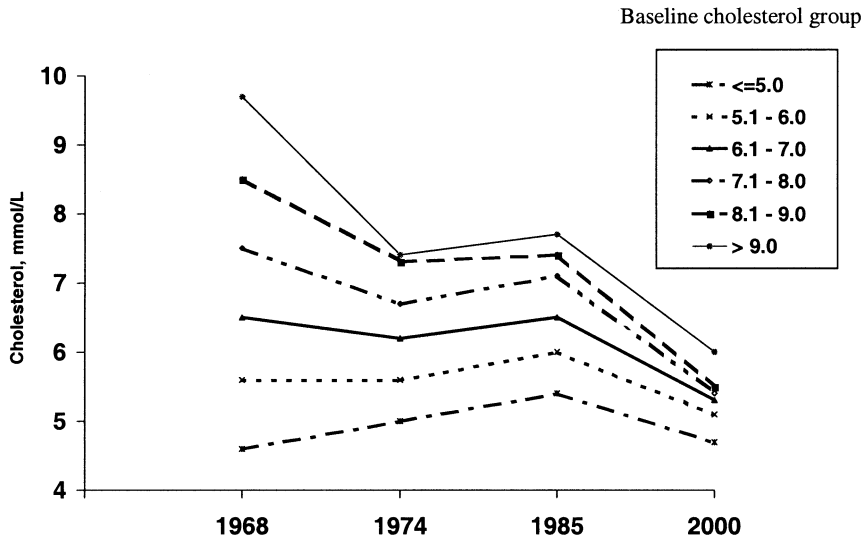

Figure 2. Distribution and change of serum cholesterol (mmol/l) according to baseline cholesterol during the follow-up. The analysis was restricted to the survivors who reported their cholesterol value in 2000 (n = 1,292). Among them serum cholesterol was available at baseline (n = 1,292), in 1974 (n = 984), and in 1985 (n = 696). At all time points the differences between the baseline cholesterol groups were highly significant (p < 0.0001).

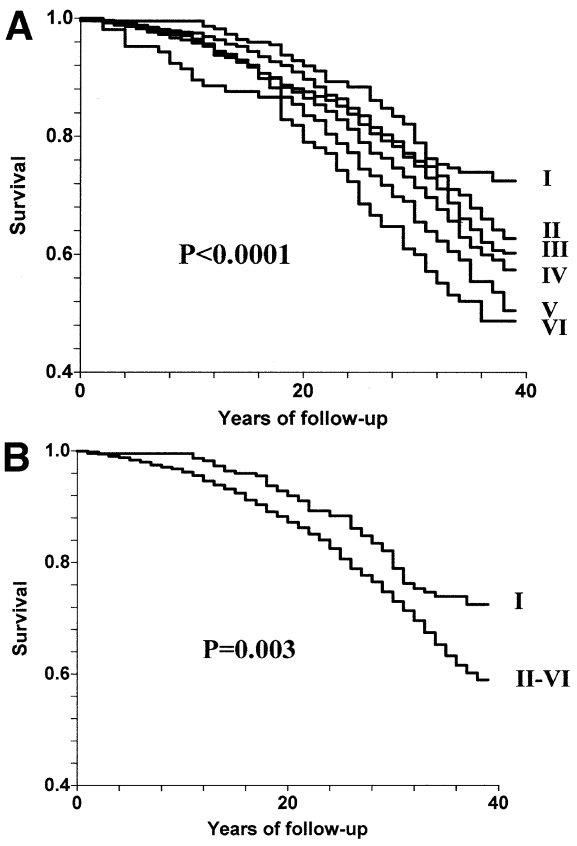

Figure 3. Survival curves of all baseline cholesterol groups (**A**, n = 3,277) and the lowest cholesterol group (≤5.0 mmol/l, n = 224) versus other groups combined **(B)**. p value in both panels denote the significance of the survival differences between the cholesterol groups (log-rank test). I: ≤5.0 mmol/l (n = 224), II: 5.1 to 6.0 mmol/l (n = 803), III: 6.1 to 7.0 mmol/l (n = 1,170), IV: 7.1 to 8.0 mmol/l (n = 720), V: 8.1 to 9.0 mmol/l (n = 255), VI: >9.0 mmol/l (n = 105).

age only or for age and cardiovascular risk factors, every 1-mmol/l increase of baseline cholesterol increased mortality risk by 11% (Table 2). The comparison between the lowest cholesterol groups and other groups combined was associated with 25% lower mortality, and the relative hazard was quite insensitive to the inclusion of a number of covariates (Table 2).

2000 survey of risk factors, morbidity, and QoL. Among survivors (average age 73 years, standard deviation 4), the response rate in 2000 was 80.9% (n = 1,820). Age and baseline cholesterol concentrations were identical in respondents and non-respondents. Men of the lowest baseline cholesterol group (≤5.0 mmol/l, n = 144) reported less coronary heart disease (p = 0.002) and cerebrovascular disease (p = 0.04) than men of the other groups combined, whereas self-reported prevalences of diabetes, cancer, and mental diseases were not statistically different (Table 3). Altogether, 84% of the men had some regular medication, and 16% used cholesterol-lowering drugs (statins).

Summary scores of the health-related QoL instrument (RAND-36) in the lowest versus combined other cholesterol groups are shown in Figure 4. All the differences prevailed after the effect of multiple comparisons was taken into account. Physical component score (PCS, adjusted for age, baseline smoking, BMI, and blood pressure) was significantly better in the lowest cholesterol group (47.6 vs. 45.4 in other groups combined, p = 0.02), whereas the MCS was similar between the cholesterol groups (52.3 vs. 52.9 in other groups combined, p = 0.51). If the lowest cholesterol group was split in half, PCS was even better in the <4.7 mmol/l group (average PCS 48.9), but the difference with the 4.7 to 5.0 mmol/l group (average PCS 47.1) was not statistically significant (p = 0.2).

DISCUSSION

The results in this homogenous, and now elderly, male population show that during almost 40 years of follow-up, serum cholesterol significantly and in a graded fashion predicted total mortality. Although original cholesterol differences had largely leveled off in the old survivors, the men with cholesterol level ≤5.0 mmol/l at baseline had the best prognosis. Besides better survival, low cholesterol was also associated with better health-related QoL in old age.

This is one of the longest follow-up studies of serum cholesterol, and the results are based on a relatively large cohort of men. They were healthy (no cardiovascular diseases or diabetes) and without hypolipidemic medications at baseline, and in midlife cholesterol level was not yet associated with subjective health or physical fitness. Mortality follow-up with national registers was reliable and during the 39-year follow-up there were a substantial number of

Table 2. Multivariate Relative Hazard of 39-Year Mortality According to Baseline Cholesterol in the Total Cohort (n = 3,277)

	Relative Hazard*		
Baseline Cholesterol	**Model A**	**Model B**	**Model C**
Continuous variable, per 1 mmol/l	1.11 (1.05–1.16)	1.11 (1.06–1.17)	1.09 (1.04–1.15)
p Value	< 0.0001	< 0.0001	0.001
≤5.0 mmol/l (n = 224)	0.76 (0.59–1.00)	0.75 (0.57–0.98)	0.72 (0.53–0.97)
p Value	0.05	0.04	0.04

*Relative hazard calculated using the Cox proportional hazards model (with 95% confidence interval). Model A: adjusted for age. Model B: adjusted for age, body mass index, and the year of first cholesterol measurement. Model C: adjusted for age, body mass index, smoking, systolic blood pressure, 1-h glucose (log transformed), and the year of first cholesterol measurement.

Table 3. Self-Reported Risk Factors and Diseases in Study Groups in 2000 by the Baseline Cholesterol Level

	Cholesterol ≤ 5.0 mmol/l (n = 144)	Cholesterol ≥ 5.0 mmol/l (n = 1,667)	p Value
Body mass index, kg/m^2	26 (4)	26 (4)	0.67
Systolic blood pressure, mm Hg	144 (16)	143 (16)	0.53
Diastolic blood pressure, mm Hg	82 (11)	82 (17)	0.57
Cholesterol, mmol/l*	4.7 (0.7)	5.3 (1.0)	<0.0001
Glucose, mmol/l	5.5 (0.9)	5.6 (1.3)	0.88
Smokers, %	9	7	0.35
Alcohol consumption, gs/week	101 (111)	125 (142)	0.22
No regular exercise, %	15	21	0.08
Diabetes, %	8	12	0.19
Coronary heart disease, %	11	24	0.002
Congestive heart failure, %	14	15	0.68
Cerebrovascular disease, %	7	14	0.04
Peripheral artery disease, %	13	17	0.29
Cancer, %	16	15	0.73
Pulmonary disease, %	5	10	0.07
Musculoskeletal disease, %	20	27	0.05
Mental disease, %	2	4	0.22
Any chronic disease, %	64	70	0.13

Data for continuous variables are mean (SD). *Reported by 89 and 1,203 men in the low and high cholesterol groups, respectively.

deaths. Health-related QoL was measured with an international instrument, validated also for the Finnish population. The cohort was homogenous, with all men from the highest social class, eliminating the possibly important confounding effect of socioeconomic status.

Our results both support and extend earlier studies. In addition to shorter but very large follow-up studies, such as the Multiple Risk Factor Intervention Trial population (16), other truly long-term studies (over 20 years) have demonstrated that cholesterol predicts not only cardiovascular mortality but also total mortality (17–19). More dispute has arisen regarding the association of low cholesterol and mortality in elderly persons. For example, in the Honolulu Heart Program (5) low cholesterol was associated with greater mortality risk. Obvious explanations for the association are intervening factors that both increase mortality risk and decrease the cholesterol level. In the nine-year follow-up of the Helsinki Aging Study, mortality risk was associated with both lowered cholesterol synthesis and lowered cholesterol absorption (20), which reflect terminal decline and lead to lower serum cholesterol levels. These associations are not identified, and the relationship between cholesterol and mortality becomes distorted unless the follow-up is long enough. Figure 2 demonstrates that quite normal cholesterol levels in old age may have been substantially higher in the same individuals earlier in life. This development of decreasing levels may have a variety of underlying explanations. Besides intervening conditions, such as chronic diseases, which lower serum cholesterol, the trend between 1968 and 1974 is mostly due to regression to the mean. From 1974 onward a contributing factor is the secular lowering trend of cholesterol levels observed in the Finnish population in recent decades (21). In the whole cohort, the use of cholesterol-lowering drugs was negligible during the major part of the follow-up; in the 1985 survey only 3% used these medications. However, their use has obviously contributed to the latest cholesterol values, as 16% of men reported use of cholesterol-lowering drugs (statins) in the 2000 survey.

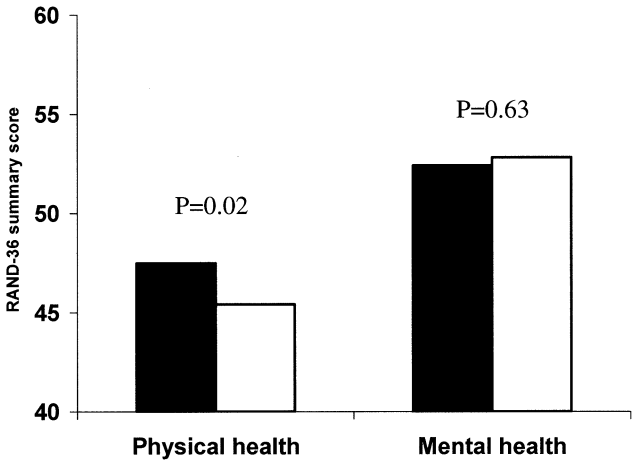

Figure 4. Baseline cholesterol and health-related quality of life (RAND-36, adjusted for age and baseline body mass index, systolic blood pressure, and smoking) in old age in 2000. The original physical component summary and the mental component summary scores were calculated according to the RAND-36 scales as described in Methods. **Solid bars** = cholesterol ≤5.0 mmol/l; **open bars** = >5.0 mmol/l.

Much debate has arisen as to whether and to what extent low cholesterol is associated with unwanted side effects; for example, adverse effects on mental functioning have been suspected (8,9). Our results on the health-related QoL do not corroborate these fears. Instead, there are significantly

better scores reflecting physical functioning in old age in men with lowest cholesterol values at baseline. In all, the PCS was significantly better in men with low cholesterol. According to the calculated norms (15), the 2-point difference in PCS between the groups in 2000 would mean a postponement of disability by 2 years in the low-cholesterol group compared with men with higher cholesterol levels. A delay of even this magnitude may have substantial impact in the expanding geriatric population. The obvious explanation for less disability is that there is less cardiovascular disease, especially coronary heart disease, among men with low cholesterol. However, it is equally important that low cholesterol is not associated with adverse effects on mental functioning over the long term. Again we remind that the present results apply to naturally low cholesterol levels. Strictly, these long-term results cannot be extrapolated to drug-induced cholesterol lowering, although it is now known that statins can reduce mortality at least up to eight years (22).

Some limitations of the study should be mentioned. The study population is selective, with all participants being men from the highest social class. Thus, extrapolation of the results to the general population (and especially to women) should be done cautiously. However, in the present study we examined within-group differences, which are probably less sensitive to the selective nature of the cohort. Another possible limitation of the study is that only one baseline serum cholesterol measurement was available, and the last cholesterol value (in 2000) was based on self-report of the participants. However, the tracking of serum cholesterol in survivors was good and consistent over the years. Furthermore, we measured serum cholesterol in 131 of the men in 2003, and the agreement was satisfactory between this measured value and the reported value in 2000. The proportion of men with low cholesterol ($\leq$5.0 mmol/l) at baseline was relatively small, but this was a reality in Finland (and many other western countries) 40 years ago. Quality-of-life measurements tended to be even better in men with cholesterol $<$4.7 mmol/l. Finally, the presence of various diseases in 2000 was also based on self-report. However, we validated coronary disease and stroke morbidity in this cohort up to 1990 from national registers (23), and even these older vascular events were reported to a high degree by the men in 2000 (85% of coronary events, 80% of stroke events). Overall, we think that self-report in this cohort of high social status is reliable.

In conclusion, our study shows that men with the lowest serum cholesterol levels in early midlife have the lowest total mortality during almost 40 years of follow-up. Among survivors in old age, low baseline cholesterol was associated with better physical health. Importantly, these long-term results show no adverse association between low baseline cholesterol and mental health.

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